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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,988	07/05/2001	Yuta Nakai	US-142O	1677

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
12/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/897,988	NAKAI ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a BPAI decision filed 8/11/09 reversing the 102 rejection as set forth in the office action mailed 7/28/06. However, further review of the case and IDS filed 5/6/09 necessitates a new rejection and hence reopening of the case. Specifically, applicants have provided a translation of a rejection in a similar foreign application that cites Kusomoto et al (Arch Microbiol, 2000, Vol 173, pages 390-397) and have provide a translation of a foreign abstract by Sone et al (Collection of Summaries of Lectures made at the Meeting of Japan Bioengineering Association, September 15, 1995, p.10) both of which are cited below.

Claims 1, 6, 7 and 11-14 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 7 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kojima et al (US 5,830,716; see entire document) in view of Calhoun et al (J Bacteriol. 1993 May; 175(10): 3020–3025; see entire document), Ciccognani et al (FEMS Microbiology Letters 94, 1992, page 1-6; see entire document) or Spehr et al (Biochemistry, 1999, Vol 38, pages 16261-16267; see entire document) or Kusomoto et al (Arch Microbiol, 2000, Vol 173, pages 390-397; see entire document) or Sone et al (Collection of Summaries of Lectures made at the

Meeting of Japan Bioengineering Association, September 15, 1995, p.10). **This is a new rejection.**

Kojima et al provide methods of using bacteria for production of amino acids. Cells are grown in culture wherein the target substance is produced in the culture medium and isolated thereof (see e.g. abstract). Specifically, Kojima et al teach that *E. coli* and *Coryneform* bacteria are well known in production methods of threonine, lysine and phenylalanine wherein the cells are engineered to improve production by altering a biochemical cellular pathway (see e.g. col 3. line 55-col 4, line 35).

Kojima et al description of altered biochemical pathways does not include one wherein the high energy efficiency pathways (*nuo* and cytochrome bo) and low efficiency pathway (*ndh* and cytochrome bd) are altered.

However, **Kusomoto** et al teaches that cells used for production methods of amino acids can be altered for improved amino acid production by altering the aerobic metabolism of the cell. Specifically, by deleting the low efficiency gene.

> "In order to improve the efficiency of cell growth and amino acid production, it is important to understand the aerobic energy metabolism or, more specifically, the respiratory proton pumps in the bacterium."
>
> "Cytochrome *bd*-type oxidase has been shown to have a lower H^+/O ratio than haem-copper oxidases (Miller and Gennis 1985; Puustinen et al. 1991). It has been reported that the H^+/e^- ratio is about 1 for intact cells of *C. glutamicum* with endogenous substrate. This is lower than that expected if an *aa*3-type haem-copper oxidase is operating (Kawahara et al. 1988). Thus, it is likely that deletion of the cytochrome *bd* genes would increase the H^+/e^- ratio of the respiratory chain, the efficiency of energy metabolism, and consequently the growth yield of the bacterium."

Hence, Kusomoto et al directly link increased amino acid production with the growth yield of the cell and the energy efficiency of the cell.

It is established in the art that the energy efficient pathways of a number of microorganisms comprise high and low efficiency pathways and that alteration of the pathways can increase the energy efficiency of the cells *and* alter the growth yield. High energy efficiency pathways include *nuo* which encodes NHD-I and cytochrome bo and low efficiency are *ndh* which encodes NDH-II and cytochrome bd.

For example, **Calhoun** et al teach

> "In principle, by directing the electron flux through specific respiratory components, the energetic efficiency of the E. coli respiratory chain can be varied between 4H+/e- (with NDH-1 and the bo-type oxidase) and 1H+/e- (with NDH-2 and the bd-type oxidase). Since the wild-type strain contains both NADH dehydrogenases and both terminal oxidases, the value for the H+/e- ratio must fall between these two extremes and will vary with growth conditions."

Calhoun et al assesses growth efficiency by constructing strains to use only one NADH dehydrogenase and one terminal oxidase and determines,

> "the data confirm the following expectations based on the in vitro proton translocation measurements: (i)based on the in vitro proton translocation measurements: (i)the elimination of the uncoupled NDH-2 results in increased energetic efficiency; (ii) strains that utilize the bd-type oxidase have a less-efficient respiratory chain than those using the bo-type oxidase."

Hence, Calhoun explicitly teaches that to increase growth efficiency, one would eliminate NDH-II or bd and increase bo. Results from *nuo* are not demonstrated because at the time of publication it had not been cloned. This reference nonetheless directs one to create the strains recited in claims 1, 6, 7 and 11.

Specifically, Calhoun et al explicitly and inherently teaches strains in which bo is increased, ndh II is decreased by gene disruption or both bo is increased and ndhII is deficient. Explicitly, Calhoun teaches that strains with deleted ndh-II has been created and produces cells with increased growth yield. (These strains are encompassed by Sone et al who teaches that

strains comprising bo cytochrome oxidase activity and that lack bd cytochrome oxidase activity has enhanced growth yield in *E. coli* (see Results).

By directing one to create cells with increased bo, Calhoun et al inherently directs one to increase copy number of bo. For example,

Ciccognani et al teach methods of culturing *E. coli* (RG145), which is a genetic recombinant strain in which an enzyme of the high-energy efficiency pathway was enhanced and an enzyme of low-energy efficiency was deficient. The cells contain a chromosomal deletion resulting in the inability of the cell to express *cydA* and contain a cosmid containing the *cyo* operon resulting in over expression of the cytochrome bo complex (page 2, section 3.1).

As another example, **Spehr et al** teach methods of culturing *E. coli* cells (ANN003/pAR1219), which comprise a high and low-energy efficiency respiratory chain pathway. ANN003/pAR1219 is a genetic recombinant strain in which an enzyme of the high-energy efficiency pathway was enhanced. The *nuo* operon was cloned and expressed under control of the inducible T7Φ10 promoter in *E. coli* cells.

In *KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art.

In the instant case, it is accepted that production methods of amino acids utilize *E. coli* and *coryneform* bacteria in which the cells are cultured and the produced amino acids are

excreted and isolated from the cell culture and that these methods can be improved with predictable results by applying known techniques of cellular engineering for improved energy efficiency.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use microorganisms that have been altered to have enhanced high efficiency pathways and/or deficient low energy pathways given that these modifications are taught by multiple sources such as Calhoun et al, Ciccognani et al, Spehr et al, Sone et al or Kusomoto et al with the known methods of producing amino acids using the methods reviewed by Kojima et al because Kojima et al teach that it is within the ordinary skill of the art to use *E. coli* to produce amino acids wherein the method requires culturing of and isolation from the culture of amino acids and because Calhoun et al, Ciccognani et al, Kusomoto et al, Spehr et al and Sone et al teach that production cells can be improved by altering the energy efficiency pathways of the cells and more specifically Kusomoto et al teach that the increase in energy efficiency as well as in improved growth yield is attributed to an improvement in the amino acid production in such strains. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to BPAI decision

The BPAI decision reversed the previous rejection under 35 USC 102 wherein Ciccognani et al (FEMS Microbiology Letters 94, 1992, page 1-6) and Spehr et al (Biochemistry, 1999, Vol 38, pages 16261-16267) were found to lack teachings that included "collecting said

substance from said medium". An assessment of the specification found that such a limitation is not reasonably interpreted to mean collecting cells.

Based upon this conclusion, a new rejection is set forth above that presents additional references that teach methods of amino acid production require use of *E. coli* and *Corneyform* and that these methods involve isolation of target substances such as amino acids from the media.

Applicants has newly supplied two references, Kusomoto et al (Arch Microbiol, 2000, Vol 173, pages 390-397; see entire document) and Sone et al (Collection of Summaries of Lectures made at the Meeting of Japan Bioengineering Association, September 15, 1995, p.10) that provide teachings that "it is suggested to use enzyme genes relating to the electron transfer system in the respiratory chain, in order to improve the growth of cells and to produce the useful substance, such as, amino acid, with the better energy efficiency" (see page 3 of the publication submitted in the IDS filed 5/6/09). These references demonstrate that alteration of amino acid producing strains for purposes of increased growth yield will also increase amino acid production by directing one to alter the high and low energy efficiency pathways. Such strains have been established and are well known in the art as set previously such as Ciccognioni et al and Spehr. An additional search of the art revealed additional art that supports the conclusion that the recited strains were known in the art and that their use in improving amino acid producing strains is predictable.

Conclusion

Claims 1, 6, 7 and 11-14 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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